

## **IgA1 and IgA2 immune complexes in primary IgA nephropathy and Henoch–Schönlein nephritis**

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*(Accepted for publication 23 March 1984)*

### **SUMMARY**

The distribution of IgA subclasses in IgA immune complexes (IgA IC) in sera of patients with primary IgA glomerulonephritis and Henoch–Schönlein purpura nephritis was analysed. High levels of IgA IC containing both IgA1 and IgA2 subclasses were present in correlation with the phases of clinical activity. In these nephropathies the finding of IgA subclass distribution in IgA IC similar to that found in secretions may add further support to the hypothesis that IgA IC are of mucosal origin, albeit a primary derangement of the humoral immune system in these patients cannot be disregarded.

**Keywords** primary IgA nephropathy Henoch–Schönlein nephritis pathogenesis immune complexes

### **INTRODUCTION**

Primary IgA nephropathy (pIgAGN) and Henoch–Schönlein purpura nephritis (HSGN) share similar histological, clinical and genetic features (Nakamoto *et al.*, 1978; Weiss *et al.*, 1978; Nyulassy *et al.*, 1977), the most evident being the presence of IgA in mesangial deposits and the recurrence of haematuria after mucosal infections.

Normal serum IgA consist of 80–90% IgA1 and only 10–20% IgA2 (Vaerman, Heremans & Laurell, 1968; Delacroix *et al.*, 1982), whereas IgA1 and IgA2 in secretions are produced in almost equal percentage by mucosal plasma cells (Delacroix *et al.*, 1982; André, André & Fangier, 1978). In addition secretory IgA molecules are mainly dimeric, with the two IgA monomers held together by a J chain. Therefore the IgA2 subclass and polymeric IgA have been considered as markers of mucosal origin (André *et al.*, 1978).

The systemic or mucosal origins of IgA deposited in glomeruli of patients with pIgAGN and HSGN have been attempted by analysing the IgA subclass distribution, but results were conflicting (André *et al.*, 1980; Conley, Cooper & Michael, 1980). No analysis of IgA subclasses in IgA containing circulating immune complexes (IgA IC) has so far been reported.

Since experimental models (Rifai *et al.*, 1979; Isaacs, Miller & Lane, 1981; Emancipator, Gallo & Lamm, 1983) support the hypothesis of a pathogenetic role of IgA IC in IgA nephropathies and several authors detected high levels of IgA IC in these diseases (Coppo *et al.*, 1980, 1982; Egido *et*

*al.*, 1980; Lesavre, Digeon & Bach, 1982; Stachura, Singh & Whiteside, 1981; Kauffmann *et al.*, 1980; Valentijn *et al.*, 1983), we attempted an analysis of the IgA subclass distribution in IgA IC.

The aim of our study was to investigate the systemic or mucosal origin of IgA IC in patients with pIgAGN and HSGN, and possibly to identify differences in IgA IC involved in these two diseases so similar as to be considered as single and multiple organ manifestation of a common pathogenetic mechanism, in which IgA plays a central role.

## MATERIALS AND METHODS

*Patients.* Table 1 summarizes histological and clinical data.

**pIgAGN** 63 sera from 40 patients (33 males and seven females; mean age 36.7 years, range 4–69 years) were studied. Thirty-seven sera from 27 patients were studied during a phase of clinical activity as defined by microscopic haematuria > 20 red blood cells (RBC)/high power ( $\times 400$ ) microscopic field (MF), or by proteinuria > 3 g/day. Ten sera from nine patients were studied during a phase of clinically inactive nephropathy, with haematuria < 5 RBC/MF and proteinuria < 0.5 g/day.

Twelve patients were studied sequentially during 3–36 months: the creatine levels remained unchanged in eight cases, improved in two patients who initially had an acute nephritic syndrome, and increased slowly in two cases.

**Table 1.** Basic histologic and clinical features of the patients with pIgAGN and HSGN studied

	pIgAGN	HSGN
No. of patients studied	40	19
No. of sera examined	63	36
<i>Histological data</i>		
Slight mesangial proliferation	32.5%	23.5%
Focal mesangial proliferation	27.5%	17.6%
Diffuse mesangial proliferation	40%	58.8%
Glomerular sclerosis	50%	35.3%
Florid epithelial crescents (range of glomeruli)	32.5% (3–40%)	66.6% (5–100%)
Evident necrosis and/or perivascular infiltration	2.5%	29.4%
Glomerular deposits of:		
IgA	100%	100%
C3	92.5%	100%
IgG	37.5%	29.4%
IgM	37.5%	35.3%
Fibrinogen	10%	41.2%
<i>Clinical data</i>		
Recurrent gross haematuria	60%	52.6%
Microscopic haematuria:		
< 5 RBC/MF*	15%	15.8%
5–25 RBC/MF	17.5%	47.4%
> 25 RBC/MF	67.5%	36.8%
Proteinuria:		
< 1 g/day	70%	36.9%
1–3 g/day	15%	36.8%
> 3 g/day <sup>1c</sup>	15%	26.3%
Serum creatine:		
< 1.3 mg%.	72.5%	63.2%
1.3–4 mg%	22.5%	21%
> 4 mg%	5%	15.8%

\* RBC/MF = red blood cells/high power ( $\times 400$ ) microscopic field.

HSGN 36 sera from 19 patients (11 males and eight females, mean age 27.7 years, range 5–58 years) were studied. A renal biopsy was performed in 17 cases. All patients had a history of purpuric rash, arthralgia and abdominal pain: eight patients were tested when these systemic signs were present.

Seventeen sera from seven patients were studied during a phase of activity of the nephropathy and five sera from five patients in an inactive phase, defined as for pIgAGN.

Eight patients had several determinations during 2–36 months: seven cases showed constant creatinine levels, another, with an acute nephritic syndrome and extensive crescents, worsened to uraemia.

No patients with pIgAGN or HSGN showed any clinical or serological evidence of liver disease, lupus erythematosus or idiopathic mixed cryoglobulinaemia.

*Detection of IgA IC, IgA1 IC and IgA2 IC.* A previously described conglutinin solid phase assay (Coppo *et al.*, 1980, 1982) was used to detect total IgAIC. Results were here expressed in optical density (OD) units.

IgA1 IC and IgA2 C were detected by an amplified conglutinin solid phase assay (Barnet, Carpentier & Lambert). Specific reagents against human alpha-1 and alpha-2 chains, raised in rabbits and purified as described elsewhere (Delacroix *et al.*, 1982, 1983a, Delacroix, Liroux & Vaerman, 1983b) were kindly supplied by Drs D. L. Delacroix and J. P. Vaerman, Experimental Medicine Unit, Brussels, Belgium.

Two hundred and fifty microlitres of serum, diluted 1/10 in isotonic Veronal-buffered saline containing 0.025% Tween-20, pH 7.5, were incubated in the conglutinin (7 µg/ml) coated tubes at room temperature for 2 h. After washing, 250 µl of rabbit anti-human IgA1 or IgA2 reagents diluted 1/500 were added and tubes were incubated overnight at 4°C. After washes, 250 µl of sheep anti rabbit IgG labelled with alkaline phosphatase diluted 1/150 were added and incubated for 1 h at 4°C. The tubes were washed and nitrophenylphosphate 1.5 mg/ml was dispensed as substrate. After 1 h the OD at 400 nm was read. Control tubes without serum and tubes with a standard preparation of pooled normal human sera were included in each test.

Values exceeding the upper 90% confidence limit (90th percentile) of 30 healthy people were considered as positive.

*Statistical methods.* The Mann–Whitney U test was used to draw comparison between the groups of data.

## RESULTS

### *Total IgA IC*

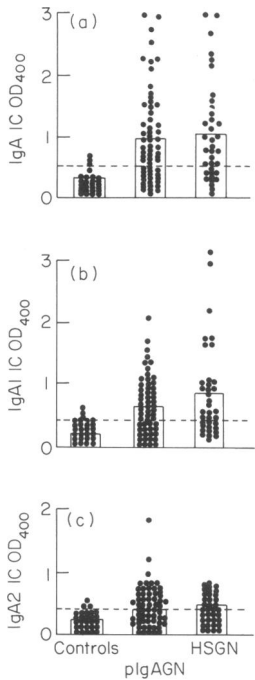
The mean levels of total IgA IC in patients with pIgAGN and HSGN included in this study were significantly higher ( $P < 0.01$ ) than those in healthy people (Fig. 1 & Table 2). Moreover the mean values obtained in HSGN were higher ( $P < 0.06$ ) than in the pIgAGN group. Positive data for IgAIC were observed in 41 of 63 (65.1%) of the sera from patients with pIgAGN and in 25 of 36 (69.4%) of the sera from HSGN.

During the phases of clinical activity, IgA IC were detected in 30 of 37 (81%) cases of pIgAGN and in all of 17 (100%) patients with HSGN. In both diseases the levels of IgA IC were found to be significantly higher during the clinical active phases than in the inactive ones ( $P < 0.01$ ) (Fig. 2 & Table 3). On comparing the levels of IgA IC observed in phases of clinically active nephropathy, significantly higher values were found in HSGN than in pIgAGN patients ( $P < 0.01$ ).

In the cases studied sequentially during the follow-up, positive data for IgA IC were found at least once in 10 of 12 (83.3%) of the patients with pIgAGN and in all eight (100%) of the patients with HSGN. Changes in IgA IC values were consensual to the clinical status: persistent high levels of IgA IC were observed in the three patients with progressing nephritis, while a gradual decrease in IgA IC values was found in the two cases improving after an acute nephritic syndrome.

### *IgA1 and IgA2 IC*

In both groups of patients the mean levels of IgA1 and IgA2 IC were found to be significantly higher



**Fig. 1.** Individual results for (a) IgA IC, (b) IgA1 IC and (c) IgA2 IC levels in sera of patients with pIgAGN, HSGN and in controls. Mean values are shown by columns. The horizontal dashed lines indicate the upper 90% confidence limit for controls.

**Table 2.** Levels of IgA IC, IgA1 IC and IgA2 IC in controls, pIgAGN and HSGN patients

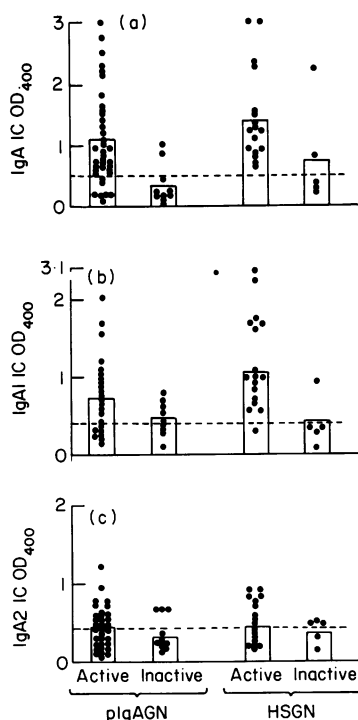
	IgA IC (OD 400 nm)	IgA1 IC (OD 400 nm)	IgA2 IC (OD 400 nm)
Controls	0.25* (0.17–0.61)† (0.50)‡	0.25 (0.10–0.65) (0.42)	0.27 (0.10–0.50) (0.43)
pIgAGN	0.91 (0.10–3.00) $P < 0.01$ §	0.64 (0.17–2.05) $P < 0.01$	0.43 (0.10–1.80) $P < 0.01$
HSGN	1.05 (0.05–3.00)	0.84 (0.14–3.15)	0.41 (0.05–0.84)

\* Mean; † range; ‡ 90<sup>th</sup> percentile; § significance of the difference with controls by the Mann–Whitney U test; ¶ significance of the difference between pIgAGN and HSGN group. NS = not significant ( $P > 0.1$ ).

( $P < 0.01$ ) than in healthy controls (Fig. 1 and Table 2). Moreover in HSGN patients the mean values of IgA1 IC, but not those of IgA2 IC, were significantly higher ( $P < 0.01$ ) than in the pIgAGN group.

Among pIgAGN patients, positive data were observed in 43 of 63 sera (68.2%), tested for IgA1 IC and in 29 of 63 sera (46%) tested for IgA2 IC. During the follow-up of 12 pIgAGN patients, IgA1 IC were detected at least once in 10 of 12 (83.3%) cases and IgA2 IC in six of 12 (50%).

Among the HSGN patients, high values of IgA1 IC were observed in 23 of 36 sera (63.8%), and



**Fig. 2.** IgA subclass distribution in IgA IC in clinically active and inactive phases of the disease. Mean values are shown by columns. The horizontal dashed lines indicate the upper 90% confidence limit for controls.

**Table 3.** Levels of IgA IC, IgA1 IC and IgA2 IC in different phases of clinical activity of pIgAGN and HSGN patients

	Clinical phase	IgA IC (OD 400 nm)	IgA1 IC (OD 400 nm)	IgA2 IC (OD 400 nm)
pIgAGN	{ activity	1.08*	0.73	0.45
		(0.10–3.00)†	(0.17–2.25)	(0.10–1.20)
	{ inactivity	0.36	0.49	0.34
		(0.15–1.00)	(0.17–0.76)	(0.10–0.60)
HSGN	{ activity	1.49	1.18	0.45
		(0.70–3.00)	(0.25–3.15)	(0.10–0.83)
	{ inactivity	0.80	0.43	0.42
		(0.25–2.25)	(0.15–0.90)	17–0.53)

\* Mean; † range; ‡ significance of the difference between data obtained in phase of active and inactive diseases. NS = difference not significant ( $P > 0.1$ ). § significance of the difference between values obtained in pIgAGN and HSGN in phases of clinical activity.

high values of IgA2 IC in 16 of 36 sera (44.4%). During the follow-up of eight HSGN patients, IgA1 IC were detected at least once in seven of eight (87.5%) cases and IgA2 IC in six of eight (75%).

During the phases of clinical activity, positive values of IgA1 IC and IgA2 IC were observed respectively in 27 of 37 sera (72.9%) and in 18 of 37 sera (48.6%) of patients with pIgAGN, and in 16 of 17 sera (94.1%) and in nine of 17 sera (52.9%), respectively, of HSGN patients.

In the pIgAGN group the difference between mean values observed in the active and inactive phases of the disease was significant for both IgA1 IC ( $P < 0.04$ ) and IgA2 IC ( $P < 0.06$ ) whereas in the HSGN group the difference was highly significant ( $P < 0.01$ ) only for IgA1 IC (Fig. 2, Table 3). Indeed in HSGN the phases of clinical activity were characterized by a striking increase in IgA1 IC and these values were significantly higher ( $P < 0.01$ ) than those observed in pIgAGN in similar phases of clinical activity.

In the two cases of pIgAGN and in the case of HSGN with an unfavourable course high values of both IgA1 IC and IgA2 IC were persistent, while there was a simultaneous decrease in both IgA IC subclasses in the two pIgAGN patients who improved clinically after an acute nephritic syndrome.

At the time the study was being made systemic signs of vasculitis were clinically evident in eight cases of HSGN together with signs of active nephritis. All these cases presented very high values of IgA1 IC (mean 1.36 OD, range 0.55–2.95), whereas the IgA2 IC values were lower (mean 0.57 OD, range 0.30–0.84).

## DISCUSSION

Following preliminary reports of increased 'heavy' IgA in sera from patients with pIgAGN and HSGN (Lopez *et al.*, 1980; Egido *et al.*, 1980), several Authors detected circulating IgA IC in these nephropathies (Lesavre *et al.*, 1982; Stachura *et al.*, 1981; Kauffmann *et al.*, 1980; Valentijn *et al.*, 1983; Coppo *et al.*, 1980, 1982) and their pathogenetical role has been seen or inferred in experimental models (Rifai *et al.*, 1979; Isaacs *et al.*, 1981; Emancipator *et al.*, 1983).

We demonstrate here high levels of circulating IgA IC in pIgAGN and in HSGN in good correlation with the clinical phases of these nephropathies, confirming our previous report in a smaller number of cases (Coppo *et al.*, 1982).

The tests made in our laboratory enable us to identify IgA IC which can bind to bovine conglutinin, mainly through C3bi present in IC. Our data appear to be in contrast with the hypothesis that the IgA IC with fixed C3bi are no longer nephrotoxic because they have been subjected to the complement releasing activity (Kauffmann *et al.*, 1980). Most likely, when IgA IC begin to circulate, they immediately fix C3b on their surface, thus initiating the two main biological activities of the complement, the releasing one—inducing the dissolution of the lattice formation into small biologically inactive fragments—and the flogistic activity—through polymorphonuclear and mononuclear cell activation—leading to tissue damage. Therefore the correlation between C3bi bearing IgA IC and clinical signs of activity, we observed above, is not surprising.

Since IgA1 and IgA2 subclasses are differently distributed between the humoral and mucosal immune system (Vaerman *et al.*, 1968; Delacroix *et al.*, 1982; Conley & Koopman, 1983; André *et al.*, 1978) we evaluated IgA subclasses in IgA IC in order to gain possible insight into the origin of IgA IC in patients with pIgAGN and HSGN.

The most important problem in evaluating the IgA subclasses derives from the availability of reagents with a satisfactory specific activity, and it has been pointed out that anti-IgA2 reagents are hard to procure and difficult to render specific, because of residual reactivity with antigens common to both subclasses (Heremans, 1974).

To overcome this impasse, the anti-IgA1 and anti-IgA2 reagents we used were previously rendered highly specific by repeated adsorptions (Delacroix *et al.*, 1982, 1983a, 1983b) to be suitable for our purpose.

In patients with pIgAGN and HSGN we found high levels of both IgA1 IC and IgA2 IC reflecting the phases of the renal disease and simultaneously increasing in phases of clinical activity.

Our finding of IgA subclass distribution in IgA IC similar to that found in secretions might add further support to the hypothesis that circulating IgA IC in these nephropathies are of mucosal origin; this would also be in agreement with some observations (Egido *et al.*, 1980) of high amounts of polymeric IgA in the serum of these patients. Nevertheless, an alternative hypothesis, based upon recent observations, can also be proposed. In healthy people (Kutteh *et al.*, 1980) and even more in pIgAGN patients (Egido *et al.*, 1982) polymeric IgA has been found to be produced by mitogen

stimulated peripheral blood lymphocytes. Precursors of IgA producing cells can differentiate equally into IgA1 and IgA2 plasma cells though they are able to secrete almost exclusively IgA1 immunoglobulins (Conley & Koopman, 1982). Moreover distinct immunoregulatory mechanisms seem to be able to enhance or suppress synthesis of one subclass or the other (Conley & Koopman, 1983; Stafford, Knight & Fanger, 1982). On the other hand the T suppressor mechanism was found to be deficient in primary IgA nephropathy (Sakai, Nomoto & Arimori, 1979), whereas the T helper cells were increased (Sakai *et al.*, 1982). These observations lead one to suppose that an unbalance of T cell activity may induce a humoral immune system response with prevalently polymeric IgA and both IgA1 and IgA2 subclasses equally represented.

Therefore our finding of the simultaneous presence of both IgA subclasses in circulating IC in these nephropathies characterized by glomerular IgA deposits is consistent with the hypothesis either of a systemic origin of IgA IC due to an unbalance in IgA specific suppressor/helper cells, or of a mucosal origin of IgA IC.

The similarities between the data obtained in pIgAGN and in HSGN, mainly the high amounts of circulating IgA IC constituted by both IgA subclasses, might provide further support for the hypothesis of a common pathogenesis of these two diseases, as suggested by several clinical and histological findings (Weiss *et al.*, 1978; Nakamoto *et al.*, 1978; Egido *et al.*, 1980).

Nevertheless HSGN differed from pIgAGN in the higher amounts of IgA IC and prevalence of IgA1 IC.

Though neither IgA subclass activates the complement classical pathway, both may activate the alternative one and IgA1 has been thought to do this more efficiently than IgA2 (Conley *et al.*, 1980). Therefore from our data one might suppose that the very high levels of IgA IC, mainly constituted by the IgA1 subclass, play a role, possibly through a greater complement activation, in inducing the vasculitic damage, a characteristic feature of the Henoch-Schönlein syndrome, lacking in primary IgA nephropathy.

We wish to thank Drs D. L. Delacroix and J. P. Vaerman, Experimental Medicine Unit, Brussels, Belgium, for kindly providing anti-IgA1 and anti-IgA2 reagents and for their advice in revising the manuscript.

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